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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,315	05/16/2005	Zhicheng Shen	60163USPCT	2385

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SYNGENTA BIOTECHNOLOGY, INC.
PATENT DEPARTMENT
3054 CORNWALLIS ROAD
P.O. BOX 12257
RESEARCH TRIANGLE PARK, NC 27709-2257

EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,315	SHEN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,50,55-64,69-78,80,90,95,97 and 98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50,55-58,63,64,69-72,80,90,95 and 97-99* is/are rejected.

7)☒ Claim(s) *59-62 and 73-78* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: search notes

DETAILED ACTION

1. Applicant's election without traverse of Group VIII in the reply filed on 6 November 2006 is acknowledged.

2. The abstract is not descriptive of the instantly claimed invention, which is a vip3C toxin. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 49-50, 55-58, 63-64, 69-72, 80, 90, 95 and 97-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a toxin of SEQ ID NO:2, 11 or 32 and methods of using it to control pests, does not reasonably provide enablement for toxins produced by expression of a nucleic acid with 93%, 95% or 96% identity to SEQ ID NO:1 or that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1, toxins with 91%, 95%, 97% and 99% identity to SEQ ID NO:2, and toxins comprising only amino acids 661-788 of SEQ ID NO:2, and methods of using the toxins to control pests. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to toxins produced by expression of a nucleic acid with 93%, 95% or 96% identity to SEQ ID NO:1 or that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1, toxins with 91%, 95%, 97% and 99% identity to SEQ ID NO:2, and toxins comprising only amino acids 661-788 of SEQ ID NO:2. The claims are also drawn to methods of using the toxins to control pests.

The instant specification, however, only provides guidance for isolation and sequencing of DNAs encoding *vip3* homologs from unidentified Bacillus thuringiensis isolates (examples 1-4); making a codon optimized version of SEQ ID NO:2 (*vip3*C) in which amino acid 738 is either a Glu or Gly - these proteins are called *vip3*C(a) and *vip3*C(b), respectively (example 5); assaying *vip3*C(a) and *vip3*C(b) for toxicity to various insects (example 6); transforming maize with the maize optimized nucleic acid and assaying their toxicity to insects (examples7-8); making hybrid toxins comprising amino acids 1-660 of vip3A and amino acids 661-788 of vip3C (example 9); prophetic DNA shuffling of vip3 genes with oligonucleotides (example 10) and prophetic high throughput screening of the resulting gene libraries (example 11); cosmid cloning of a full-length vip3C gene (example 12); bioassay of the toxin encoded by the gene - this toxin has 6 amino acid substitutions relative to SEQ ID NO:2with a slightly different sequence than SEQ ID NO:2 (example 13).

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain pesticidal activity of the encoded protein towards the insects listed in claims 80 and 97. The specification also fails to provide guidance for which amino acids can be

deleted and which regions of the protein can tolerate insertions and still produce a functional toxin.

A toxin with 91% identity to SEQ ID NO:2 has 70 amino acid substitutions relative to 788 amino acid long SEQ ID NO:2, one with 95% identity to SEQ ID NO:2 has 39 amino acid substitutions, one with 97% identity to SEQ ID NO:2 has 23 amino acid substitutions, and one with 99% identity to SEQ ID NO:2 has 7 amino acid substitutions. There are 19^{788} (8.8×10^{751}) possible single amino acid substitutions (for comparison, the estimate of the total number of atoms in the universe is 10^{81}).

Nucleic acids with 93% identity to the 2367 nucleotide long SEQ ID NO:1 would have 165 substitutions and encompass those that encode proteins with 165 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 79% identity to SEQ ID NO:2. Nucleic acids with 95% identity to SEQ ID NO:1 would have 118 substitutions and encompass those that encode proteins with 118 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 85% identity to SEQ ID NO:2. Nucleic acids with 96% identity to SEQ ID NO:1 would have 94 substitutions and encompass those that encode proteins with 94 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 88% identity to SEQ ID NO:2. Nucleic acids that hybridize to nucleotides 1981-2367 of SEQ ID NO:1 under the specified conditions could have any number of substitution nucleotides 1-1980 of SEQ ID NO:1 and an estimated 95% identity to nucleotides 1981-2367 of SEQ ID NO:1, and thus encompass those that encode proteins with up to 700 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 12% identity to SEQ ID NO:2.

The specification proposes using DNA shuffling to make the claimed proteins (examples 10-11). However, Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, the teachings of Guo et al suggests it would require undue experimentation, if it is not impossible, to produce toxins with 700, 165, 118, 95, 70, 39, 23 or 7 substitutions relative to SEQ ID NO:2 by random shuffling.

In a post-filing reference Lee et al (2003, Appl. Environ. Microbiol. 69:4648-4657) teach that the mode of action of the related Vip3A protein differs from that of the *cry* endotoxins (pg 4655, right column, paragraph 3). Further, the mode of action is complex (paragraph spanning the columns on pg 4653) and requires interaction with unidentified insect proteins (pg 4654, right column, paragraphs 1-2); the amino acids responsible for toxicity are not known. The instant specification also does not teach which amino acids are responsible for toxicity.

The amino acids required for toxicity toward different insects appears to be unpredictable. Selvapandiyan et al (2001, Appl. Environ. Microbiol. 67: 5855-5858) teach that a vip3A protein missing the first 39 amino acids of Vip3A had reduced toxicity towards one insect species, but not another (Table 3), and that three amino acid substitutions affected toxicity toward another insect species but not others (paragraph spanning ph 5857-5858).

The claims are also drawn to toxins comprising only amino acids 661-788 of SEQ ID NO:2 or produced by expression of a nucleic acid that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1. A protein comprising only these 127 amino acids is unlikely to function as a toxin.

The claims are also drawn to toxins comprising only amino acids 661-788 of SEQ ID NO:2 or produced by expression of a nucleic acid that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1. A protein comprising only these 127 amino acids is unlikely to function as a toxin.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate toxins with 700, 165, 118, 95, 70, 39, 23 or 7 amino acid substitutions relative to SEQ ID NO:2 would require undue experimentation.

As the specification does not teach the full scope of toxins with 700, 165, 118, 95, 70, 39, 23 or 7 amino acid substitutions relative to SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of proteins encompassed by the claims to identify those with toxin activity, if such toxins are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

5. Claims 49-50, 55-58, 63-64, 69-72, 80, 90, 95 and 97-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A full review of the specification indicates that insecticidal toxins are essential to the operation of the claimed invention.

The claims are directed to a genus of toxins produced by expression of a nucleic acid with 93%, 95% or 96% identity to SEQ ID NO:1 or that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1, toxins with 91%, 95%, 97% and 99% identity to SEQ ID NO:2, and toxins comprising only amino acids 661-788 of SEQ ID NO:2. The claims encompass proteins with 700, 165, 118, 95, 70, 39, 23 or 7 amino acid substitutions relative to SEQ ID NO:2.

Selvapandiyan et al (2001, Appl. Environ. Microbiol. 67: 5855-5858) teach that vip3 toxins that differ by only a few amino acids have different insect specificities (paragraph spanning ph 5857-5858). The specification only describes as amino acids 661-788 of SEQ ID NO:2, when with the entire protein, as being important for toxicity to two insect species. Beyond this, no structure is described as being required for toxin function.

The structural features that distinguish toxins with 9 with 700, 165, 118, 95, 70, 39, 23 or 7 amino acid substitutions relative to SEQ ID NO:2 from other proteins with 700, 165, 118, 95, 70, 39, 23 or 7 amino acid substitutions relative to SEQ ID NO:2 are not described in the specification. The necessary and sufficient structural elements of the claimed toxins are not described.

The only species described in the specification is SEQ ID NO:2, 11 and 32; SEQ ID NO:s 11 and 33 differ from SEQ ID NO:2 by only 6 amino acids.

One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, the disclosed species are insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described toxins produced by expression of a nucleic acid with 93%, 95% or 96% identity to SEQ ID NO:1 or that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1, toxins with 91%, 95%, 97% and 99% identity to SEQ ID NO:2, and toxins comprising only amino acids 661-788 of SEQ ID NO:2 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 49, 70, 80, 90, 95 and 97-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Schnepf et al (US Patent 6,369,213, filed July 1997).

Schnepf et al disclose a toxin produced by expression of a nucleic acid with 92.9% identity to SEQ ID NO:1 (their SEQ ID NO:83, which encodes their SEQ ID NO:82, see search results). There are only 3 nucleotides that differ between a nucleic acid with 93% identity to SEQ ID NO:1 and one with 92.9% identity to SEQ ID NO:1. A mere 3 degenerate codon

substitutions separate these two nucleic acids. Thus, the toxin taught by Schnepf et al would be made by a nucleic acid with 93% identity to SEQ ID NO:1.

The toxin taught by Schnepf et al would toxic to one of the pests listed in the instant claim 80, and the supernatant from the PS86BB1 strain that produces the toxin would be an insecticidal composition comprising it (column 21, lines 3-10). Schnepf et al also teach a method of controlling insects, including *Agrotis ipsilon* and *Heliothis virescens*, comprising orally delivering to the insects an effective amount of the toxin (column 29, line 44, to column 31, line 20).

Claim Rejections - 35 USC § 102 / 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 71-72 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Schnepf et al (US Patent 6,369,213, filed July 1997).

Schnepf et al disclose a toxin produced by expression of a nucleic acid with 92.9% identity to SEQ ID NO:1 (their SEQ ID NO:83, which encodes their SEQ ID NO:82, see search results). There are 50 nucleotides that differ between a nucleic acid with 95% identity to SEQ ID NO:1 and one with 92.9% identity to SEQ ID NO:1 and 4 that differ between a nucleic acid with 96% identity to SEQ ID NO:1 and one with 92.9% identity to SEQ ID NO:1. It would appear

that the toxin taught by Schnepf et al could be encoded by a nucleic acid with 95% or 96% identity to SEQ ID NO:1, if degenerate codons are taken into account.

Alternately, if the toxin taught by Schnepf et al could not be encoded by a nucleic acid with 95% or 96% identity to SEQ ID NO:1, if possible to do so, it would be obvious to one of obvious skill in the art to make amino acid substitutions in the toxin, and therefore nucleotide substitutions in the toxin, taught by Schnepf et al because of the suggestion of Schnepf et al to do so (column 11, line 43, to column 12, line 18).

Claim Rejections - 35 USC § 103

10. Claims 49, 55-58, 70, 80, 90, 95 and 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnepf et al (US Patent 6,369,213, filed July 1997) in view of Stemmer et al (US Patent 6,500,617, filed May 1998).

The claims are drawn to a toxin with 91%, 95%, 97% or 99% identity to SEQ ID NO:2.

Schnepf et al disclose a toxin with 90.6% identity to SEQ ID NO:2 (their SEQ ID NO:82, see search results). The other teachings of Schnepf et al are discussed above. Schnepf et al do not disclose a toxin with 91%, 95%, 97% or 99% identity to SEQ ID NO:2.

Stemmer et al teach a method of making variants in pest resistance genes (claims 1 and 25)

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the toxin taught by Schnepf et al to use the method of Stemmer et al to make variants of their toxin, thereby making a toxin with 91%, 95%, 97% or 99% identity to SEQ ID NO:2. One of ordinary skill in the art would have been motivated to do so because Schnepf et al

suggest making amino acid substitutions in the toxin, (column 11, line 43, to column 12, line 18) and because Stemmer et al teach making variants of other vip proteins (claim 25). Schnepf et al suggest making toxins with 60% identity to theirs; as their toxin is 789 amino acids long, a toxin with 60% identity to it would have 315 amino acid substitutions. A toxin with 90.6% identity to SEQ ID NO:2 differs from one with 91% identity to SEQ ID NO:2 by 4 amino acid substitutions, differs from one with 95% identity to SEQ ID NO:2 by 29 amino acid substitutions, differs from one with 97% identity to SEQ ID NO:2 by 51 amino acid substitutions, and differs from one with 99% identity to SEQ ID NO:2 by 67 amino acid substitutions. Thus, if it is possible to make the claimed toxins (see the enablement rejection above), the claimed toxins are within the genus of those suggested by Schnepf et al.

11. Claims 59-62 and 73-78 are free of the prior art, given the failure of the prior art to teach or suggest an isolated toxin of SEQ ID NOs: 2, 11 or32. Claims 50, 63-64 and 69 are free of the prior art, given the failure of the prior art to teach or suggest an isolated toxin of amino acids 661-788 of SEQ ID NO:2 or encoding a nucleic acid that hybridizes to nucleotides 1981-2367 of SEQ ID NO:1.

12. Claims 59-62 and 73-78 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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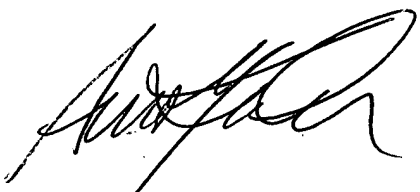
Anne Kubelik, Ph.D.
January 18, 2007



ANNE KUBELIK, PH.D.
PRIMARY EXAMINER